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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
HADDAD, MAHER M

ART UNIT	PAPER NUMBER
1644	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,439	SERRE ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- Th MAILING DATE of this communication appears on the cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *4,6,8 and 9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,7 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-10 are pending.

2. Applicant's election with traverse of Group I, claims 1-3, 5, 7 and 10 drawn to a citrullinated polypeptide derived from all or part of the sequence of the α-chain of a vertebrate fibrin by substitution of at least one arginine residue with a citrulline residue an antigenic composition, and a kit filed on 6/9/03, is acknowledged.

Applicant's traversal is on the grounds that the instant application is a 371 of International Application PCT/FC00/01857, filed June 30, 2000, and is properly subject to restriction only under the PCT rules. See the PCT administrative Instructions in M.P.EP, annex B, part 1, which provides direction on restriction practice under the PCT rules. Thus the restriction practice is not applicable to a national stage application such as the present application. While the Examiner Acknowledge that the application is a 371 of PCT/FR00/01857 and restriction practice under 35 U.S.C. 121 should not be used. However, Applicant's inventions do not contribute a special technical feature when viewed over the prior art they do not have a single general inventive concept and so lack unity of invention as set forth in below of this instant Office Action.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 4, 6, and 8-9 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 1-3, 5, 7 and 10 are under examination as they read on a citrullinated polypeptide derived from all or part of the sequence of the a-chain of a vertebrate fibrin by substitution of at least one arginine residue with a citrulline residue an antigenic composition, and a kit.

5. The claim to priority to PCT/FR00/01857, filed 06/30/2000, disclosed in the Oath/Declaration, needs to be included as the first sentence of the specification following the title.

6. 35 U.S.C. § 101 reads as follows:

> *"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".*

7. Claims 1-3, 5, 7 and 10 are rejected under 35 USC 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-3, 5, 7 and 10, as written, do not sufficiently distinguish over citrullinated polypeptides as they exist naturally because the claims do not particularly point out any non-naturally

occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Purified" as disclosed on page 14, line 23 of specification. See MPEP 2105.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. It is improper to recite "labeled with and/or conjugated to a carrier molecule" in claim 5, line 3. It is unclear how the citrullinated polypeptide would be labeled and conjugated to a carrier at the same time. It is suggested that "and/or" be changed to "or".

The "complement of the cDNA" recited in claims 3-5 has no antecedent basis in base claim 1. Base claim 1 only recites a cDNA.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-3, 5, 7 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a purified citrullinated polypeptide of α-chain of SEQ ID NO: 1 of a mammalian fibrin, by substitution of at least one arginine residue with a citrulline residue, a composition and a kit thereof for the diagnosing the presence of rheumatoid arthritis does not reasonably provide **enablement** for any citrullinated polypeptide derived from all or part of the sequence or the α-chain of any vertebrate fibrin, by substitution of at least one arginine residue with a citrulline residue in claim 1, wherein the citrullinated polypeptide derived from a sequence of at least 5 consecutive amino acids of the α-chain of a vertebrate fibrin in claim 2, any antigenic composition for diagnosing the presence of rheumatoid arthritis-specific autoantibodies in a biological sample, characterized in that it contains at least on citrullinated polypeptide optionally labeled with and/or conjugated to a carrier molecule in claim 5 or a pharmaceutical composition, characterized in that it contains as active principle, at least one citrullinated polypeptide in claim 10. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

The specification does not provide a sufficient enabling description of the claimed invention. The specification discloses only two citrullinated amino acid sequences, SEQ ID NO:1 that was obtained from the membrane fragment corresponding to the w64-78 antigen. SEQ ID NO:1 disclosed to be identical to the sequence 36-46 of the product of the human fibrinogen α-chain precursor gene (page 12, lines 9-15. The second citrullinated amino acid is SEQ ID NO: 2 which was obtained from the membrane fragment corresponding to the center of the immunoreactive zone corresponding to the w55-61 antigen. SEQ ID NO:2 is disclosed to be identical to the sequence 45-54 of the product of the human fibrinogen β-chain precursor gene (e.g., page 12 at lines 21-26). The instant claims encompass in their breadth *any* polypeptide "derived from all or part of the α-chain" of *any* vertebrate fibrin, wherein the citrullinated polypeptide derived from a sequence of at least 5 consecutive amino acids of the α-chain.

However, there does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the various polypeptides recited in the instant claims. A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. There is insufficient guidance to direct a person of skill in the art to select particular sequences or sequence lengths as essential for diagnosing the presence of rheumatoid arthritis. Without detailed direction as to which amino acid sequences are essential to the function of the polypeptide, a person of skill in the art would not be able to determine without undue experimentation which of the plethora of amino acid sequences encompassed by the instant claims would share the ability to diagnose RA. Further, the claims encompass fibrin sequences that contained no arginine.

Taresa et al (J. Biol. Chem., 1996; 271:30709-30716) teach that "the ureido group on the citrulline formed by the peptidylarginine deiminase enzyme modification functions to unfold proteins due to decrease in net charge, loss of potential ionic bonds, and interference with H bonds" (see abstract in particular). Taresa et al further teaches that arginines located near the amino terminus are poorly modified, arginines in highly α-helical protein structures are only slowly modified to near completion and arginines in proteins of little structural order are rapidly modified to near completion. The PAD reaction is dependent on both substrate structure and precise sequence around the arginine residues (see page 30714 l, 2nd col., last paragraph). Thus it is unpredictable if partial citrullination of arginine residues result in an extensive charge heterogeneity would share any functional activity by two polypeptides having 100% identity over the full length of their sequences.

Schellekens et at., (J. Clin. Invest., 1998, 101:273-281) teach that genetic susceptibility to RA is associated with the presence of certain subsets of HLA class II DR1 and DR4 that are believed to be involved in presenting T cell epitopes that are associated with joint inflammation (see page 279, col., 2nd ¶). However, the length of the peptide is important for binding to HLA (along with the presence of anchor (or "motif") amino acid residues present within the peptide). The peptides

that bind to class II molecules have a predominant length. Accordingly, there is a high level of unpredictability in designing/selecting amino acids of the α-chain of a vertebrate fibrin sequences that would still maintain binding function, and applicant does not provide direction or guidance to do so. Therefore, the identification of amino acids antigen that bears citrulline-containing polypeptide that is able to induce an RA-specific HLA class II-restricted T cell proliferation is unpredictable.

Also, at issue is whether or not the claimed composition would function as pharmaceutical composition. In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the pharmaceutical composition as claimed, and absence of working examples providing evidence which is reasonably predictive that the claimed pharmaceutical composition are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed pharmaceutical composition with a reasonable expectation of success.

In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Since no animals were used as model system to treat a RA. It is not clear that reliance on the *in vitro* data of reactivity of rheumatoid sera accurately reflects the relative mammal efficacy of the claimed therapeutic strategy. The specification does not adequately teach how to effectively treat a rheumatoid arthritis or reach any therapeutic endpoint in mammals by administrating the pharmaceutical composition. The specification does not teach how to extrapolate data obtained from an in vitro assay studies to the development of effective in vivo mammalian therapeutic treatment, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the pharmaceutical composition.

The specification does not provide sufficient teaching as to how it can be assessed that treatment of rheumatoid arthritis in the assay was achieved after the administration of the pharmaceutical composition of the invention.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

9. Claims 1-3, 5, 7 and 10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a purified citrullinated polypeptide of α-chain of SEQ ID NO: 1 of a mammalian fibrin by substitution of at least one arginine residue with a citrulline residue, a composition and a kit thereof for the diagnosing the presence of rheumatoid arthritis.

Applicant is not in possession of any citrullinated polypeptide derived from all or part of the sequence or the α-chain of any vertebrate fibrin, by substitution of at least one arginine residue with a citrulline residue in claim 1, wherein the citrullinated polypeptide derived from a sequence of at least 5 consecutive amino acids of the α-chain of a vertebrate fibrin in claim 2, any antigenic composition for diagnosing the presence of rheumatoid arthritis-specific autoantibodies in a biological sample, characterized in that it contains at least on citrullinated polypeptide optionally labeled with and/or conjugated to a carrier molecule in claim 5 or a pharmaceutical composition, characterized in that it contains as active principle, at least one citrullinated polypeptide in claim 10.

Applicant has disclosed only amino acid of SEQ ID NO: 1 and SEQ ID NO: 2; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

11. Claims 1-3, 5 and 10 are rejected under 35 U.S.C. 102(a) as being anticipated by Masson-Bessiere et al (Rev. Rheum., December 1999, 66:754).

Masson-Bessiere et al teach 64-78 citrullinated polypeptide derived from α-chain of human fibrin. Masson-Bessiere et al further teach that a 11 amino acid sequence was obtained from the 64-78KD protein. The sequence was identical to the 36-46 human α-chain of fibrinogen. Masson-Bessiere et al, show that using purified human fibrinogen, α chain is recognized by affinity-purified AFA, by AFA+ sera and by a noticeable proportion of AFA-sera, only if the protein has been previously deiminated.

Masson-Bessiere et al concluded that the target antigens of AFA in the rheumatoid synovial tissue are deiminated form of the α chain of fibrin (see abstract page 754 in particular).

Claims 5 and 10 are included because the claims read on the active or essential ingredients of the citrullinated polypeptide.

The reference teachings anticipate the claimed invention.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Masson-Bessiere *et al* in view of U.S. Patent No. 5,858,723.

The teachings of Masson-Bessiere et al reference have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of optionally labeled with and/or conjugated to a carrier molecule in claim 5.

The `723 patent teaches methods for diagnosing diseases associated with the expression of HERV-K10 gag and/or env proteins, such as seminoma, by detecting antibodies that bind specifically to the polypeptides. The `723 patent further teaches that the polypeptide may be attached or conjugated to a carrier molecule or solid phase. After a period of contact between the sample and the polypeptide, during which antibodies in the sample are bound to the polypeptide, unbound antibodies are washed away. The bound antibodies are then visualized or otherwise detected by adding a compound or compounds that detect the antibodies which are specifically bound to the polypeptides (see col., 10, lines 6-23 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to optionally conjugate the citrullinated polypeptide taught by Masson-Bessiere et al to a carrier molecule as taught by the `723 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such conjugate allow for the diagnosing diseases associated the citrullinated polypeptide derived from the α-chain fibrin as taught by `723 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Masson-Bessiere *et al* in view of U.S. Patent No. 4,281,061.

The teachings of Masson-Bessiere et al reference have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of a kit for detecting rheumatoid arthritis-specific autoantibodies in biological sample, characterized in that

it comprises at least one polypeptide and also buffers and reagents suitable for constituting a reaction medium which allows the formation of an antigen/antibody complex, and/or means for detecting said antigen/antibody complex in claim7.

The `061 patent teaches that reagents for an immunoassay can be provided as kits as a matter of convenience and to optimize the sensitivity of the assay in the range of interest (col 22, line 62 - col 23, line 4).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include the necessary reagents to perform the detection assay in a kit format as taught by the `061 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so for the convenience and economy of the user as taught by the `061 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. Claim 1-3 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,821,068 in view of Schellekens et al.

The `068 patent teaches a human soluble α-fibrin and fibrin fragments such as GP**R**VVE**R**HQS (see col., 1 lines 28-34, col., 10, table I and col., 15, patented SEQ ID NO:2, in particular). The `068 further teaches that the fibrin monomers can be present in blood up to a cetain level as a soluble fibrin formed by binding with fibrinogen in blood. (col., 1 lines 33-35 in particular)

The claimed invention differs from the reference teachings only by the recitation of a citrullinated polypeptide by substitution of at least one arginine residue with a citrulline residue in claim 1, an antigenic composition for diagnosing the presence of rheumatoid arthritis-specific autoantibodies in a biological sample, characterized in that it contains at least one citrullinated polypeptide , optionally labeled with and/or conjugated to a carrier molecule in claim 5.

Schellekens et al teach peptidylarginine deiminase that modifies arginine in a peptide context to citrulline. Schellekens et al further teach that the enzyme is expressed in a broad range of tissues and cell types, suggesting that deimination of arginine within proteins is not a rare phenomenon. Further, Schellekens et al teach that the enzyme is present in synovial cells is likely, and its presence in hematopoietic cells types known to infiltrate the synovium during joint inflammation. Schellekens et al further suggest that the deimination can play a role in the breakage of inter- and intramolecular interations, thereby making proteins more susceptible to

the activity of proteolytic enzymes (see page 280, 1st col., 3¶). Schellekens et al further teach that in principle, the early presence of APF/AKA antibodies, pointing very specifically to the development of RA, can be determined by ELISA using synthetic peptides that contain citrulline (see page 280, last ¶ in particular). Schellekens et al suggested the identification of peptides with enhanced binding characteristics to the APF/AKA autoantibodies. The identification of such peptides with not only enhance their diagnostical usefulness, but will also provide more precise information on the nature of the antigenic determinants responsible for the specific occurrence of APF/AKA antibodies in RA sera (see page 280, last ¶ in particular).

Given the presence of the peptidylarginine deiminase in the hematopoietic cells, it would have been obvious to one of ordinary skill in the art at the time the invention was made to find deiminated the α-chain polypeptide using APF/AKA antibodies as taught by the Schellekens et al and obtain them as a citrullinated α chain polypeptide.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the modification and the identification of such peptides will not only enhance their diagnostical usefulness, but will also provide more precise information on the nature of the antigenic determinants responsible for the specific occurrence of APF/AKA antibodies in RA sera as taught by the schellekens et al.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,821,068 in view of Schellekens et al as applied to claims 1-3 and 10 above, and further in view of U.S. Patent No. 5,858,723.

The teachings of the `068 and `723 patents and schellekens et al reference have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of optionally labeled with and/or conjugated to a carrier molecule in claim 5.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to find the citrullinated α-chain fibrin and optionally conjugate the citrullinated polypeptide to a carrier molecule as taught by the `723patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such conjugate allow for the diagnosing diseases associated the citrullinated polypeptide derived from the α-chain fibrin as taught by `723 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,821,068 in view of Schellekens *et al* as applied to claims 1-3, 5 and 10 above, and further in view of U.S. Patent No. 4,281,061.

The teachings of `068 patent and Schellekens *et al* reference have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of a kit for detecting rheumatoid arthritis-specific autoantibodies in biological sample, characterized in that it comprises at least one polypeptide and also buffers and reagents suitable for constituting a reaction medium which allows the formation of an antigen/antibody complex, and/or means for detecting said antigen/antibody complex in claim7.

The `061 patent teaches that reagents for an immunoassay can be provided as kits as a matter of convenience and to optimize the sensitivity of the assay in the range of interest (col 22, line 62 - col 23, line 4).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include the necessary reagents to perform the detection assay in a kit format as taught by the `061 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so for the convenience and economy of the user as taught by the `061 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
August 11, 2003

Christina Chan

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600